

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Patent No.: US RE37,504

Dated: January 8, 2002

Atty Docket No.: 62-575

RE REISSUE PATENT OF:

LIN

TITLE: OPHTHALMIC SURGERY METHOD USING NON-CONTACT SCANNING LASER

January 14, 2002

PETITION FOR CERTIFICATE OF CORRECTION
DUE TO PATENT OFFICE ERROR

Director of the US Patent & Trademark Office
Washington, DC 20231

Sir:

We recently received the original letters Patent RE37,504. However, in our review of the claims of that patent, we note a typographical error in Claim 56. Please correct RE37,504 by issuing the attached Certificate of Correction.

Respectfully submitted,

William H. Bollman
Reg. No. 36,457

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CERTIFICATE
JAN 16 2002
OF CORRECTION



UNITED STATES PATENT AND TRADEMARK OFFICE

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DATE: January 2, 2003
TO: Certificates of Correction Branch
FROM: Linda Dvorak
SPE, Art Unit 3739
SUBJECT: REQUEST FOR CERTIFICATE OF CORRECTION

Please issue a Certificate of Correction in U. S. Letters Patent No. RE37,504 as specified on the attached Certificate.

A handwritten signature in black ink, appearing to be "Linda Dvorak", written over a horizontal line.

Linda Dvorak, SPE
Art Unit 3739

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE

Patent No. RE37,504

Patented: January 8, 2002

It is requested that the first line of the specification of this patent be amended to make reference to a Continuing Reissue application which claims the benefit of the instant patented file. The first line of the specification of the patent should be amended to read as follows:

“This application is a continuation-in-part application of Serial No. 07/985,617, filed December 3, 1992, now abandoned. This application is also related to U.S. Serial No. 10/034,929, filed January 4, 2002 which is a continuation application of the instant patented file.”

A handwritten signature in black ink, appearing to read 'Linda Dvorak', is written over a horizontal line.

Linda Dvorak
Supervisory Patent Examiner,
Art Unit 3739

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : RE 37,504 E
DATED : January 8, 2002
INVENTOR(S) : Lin

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 21,

Line 62, change "claim 54" to -- claim 68 --.

Signed and Sealed this

Twenty-seventh Day of May, 2003

A handwritten signature in black ink, appearing to read "James E. Rogan", with a horizontal line drawn underneath it.

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO : ⁹US RE37,504 ^E
DATED : January 8, 2002
INVENTOR(S) : Lin

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

col. 2, line 62

~~Please change claim 56 as follows:~~

~~line 2~~ change "claim 54" to -- claim 68 --.

MAILING ADDRESS OF SENDER:

William H. Böllman, Esq.
Manelli Denison & Selter PLLC
2000 M Street, NW Suite 700
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PATENT NO. US RE37,504

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4193985



UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas, THERE HAS BEEN PRESENTED TO THE
Commissioner of Patents and Trademarks

A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATIONS OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED HAVE BEEN COMPLIED WITH, AND THE TITLE THERETO IS, FROM THE RECORDS OF THE PATENT AND TRADEMARK OFFICE IN THE CLAIMANT(S) INDICATED IN THE SAID COPY, AND WHEREAS, UPON DUE EXAMINATION MADE, THE SAID CLAIMANT(S) IS (ARE) ADJUDGED TO BE ENTITLED TO A PATENT UNDER THE LAW.

NOW, THEREFORE, THESE Letters Patent ARE TO GRANT UNTO THE SAID CLAIMANT(S) AND THE SUCCESSORS, HEIRS OR ASSIGNS OF THE SAID CLAIMANT(S) FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT, SUBJECT TO THE PAYMENT OF ISSUE FEES AS PROVIDED BY LAW, THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE UNITED STATES.

In testimony whereof I have hereunto set my hand and caused the seal of the Patent and Trademark Office to be affixed at the City of Washington this *eighteenth* day of *March* in the year of our Lord one thousand nine hundred and *eighty*, and of the Independence of the United States of America the two hundred and fourth.

Attest:

John G. Darnall
Attesting Officer.

William H. Diamond
Commissioner of Patents and Trademarks.

- [54] MULTIPLE-UNITS DRUG DOSE
- [75] Inventors: Helle Bechgaard, Hellerup; Arne M. Pedersen, Vanlose, both of Denmark
- [73] Assignee: A/S Alfred Benzon, Copenhagen, Denmark

[21] Appl. No.: 889,269

[22] Filed: Mar. 23, 1978

[30] Foreign Application Priority Data

Mar. 30, 1977 [GB] United Kingdom 13296/77

[51] Int. Cl.² A61K 9/22; A61K 9/54

[52] U.S. Cl. 424/19; 424/24;
424/14; 424/16; 424/20; 424/32; 424/33;
424/35

[58] Field of Search 424/24, 14, 16, 19-22,
424/32, 33, 35

[56] References Cited

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Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Merriam, Marshall & Bicknell

[57]

ABSTRACT

A controlled release multiple-units drug dose is described, which comprises a tablet or a capsule enclosing a plurality of subunits, each containing a therapeutically active agent and being enclosed in an insoluble membrane allowing for diffusion of the juices of the gastrointestinal tract, at least some of the subunits being of increased specific weight as compared with the specific weight of the active agent.

4 Claims, No Drawings

MULTIPLE-UNITS DRUG DOSE

This invention relates to oral drug depot formulations of the multi-units type with a controlled release action of short or long duration of the active agent or agents. A multiple-units dose consists of a great number of subunits, usually in the form of pellets or microencapsulated crystals contained in a capsule or tablet.

Oral depot products can be formulated according to two different principles: The controlled release single-unit dose or the multiple-units dose.

A single-unit dose, e.g. a matrix tablet or a tablet enclosed in a diffusion membrane, is a depot which releases a drug during the passage of the entire alimentary canal without disintegrating. The empty core or shell is discharged.

A multiple-unit dose consists of a large number of mini-depots, e.g. pellets or microencapsulated crystals, contained in a capsule or a tablet. These many subunits are dispersed and distributed throughout the gastrointestinal tract when the capsule or tablet disintegrates.

An adjustment of the release rate of the depot according to its transit time through the small intestine is essential to the achievement of a satisfactory bioavailability, as the greatest absorption capacity is generally possessed by this part of the gastrointestinal tract, particularly the jejunum and the proximal ileum.

Single-unit doses tend to follow the food having a normal transit time through the small intestine that varies between 3 and 8 hours. Accordingly, 6-10 hours are recommended by many authors as the maximum duration of in vitro release from depot formulations.

In some cases it is desirable, however, to retain the drug depot in the upper gut in order (i) to assure optimal absorption or (ii) to additionally extend the absorption phase. The latter applies e.g. to drugs with biological half-lives requiring an absorption period of more than 6-10 hours to facilitate a lower dosage frequency (once daily) and thus a more secure therapy.

As the subunits of the multiple-units formulations are distributed freely throughout the gastrointestinal tract, their transport is to a greater extent independent of the transit time of food. Hence the bioavailability of these products is less vulnerable to variations in both gastric emptying and intestinal transit time, providing a more secure interaction between in vitro release and bioavailability and thus a better reproducible effect.

Accordingly, the multiple-units dose principle is expected to facilitate the production of drug depots with a reproducible and predetermined prolonged intestinal transit time.

Obviously, it would be advantageous if the absorption period could be extended in order to reduce the frequency of drug administration to, for example, once daily, thus improving patient compliance and reducing the risk of erroneous administration.

The invention is based upon the observation that the specific weight of the subunits in a multiple-units dose greatly influences the average transit time of the subunits through the gastrointestinal tract.

A pilot study showed that in the same patient an increase by 0.6 g/ml in the specific weight of the subunits (pellets or microencapsulated crystals) in a multiple-units dose increased the transit time of the subunits through the gastrointestinal tract up to 5 times, irrespectively of the size of the subunits.

An object of the invention is thus to utilize this discovery to obtain a reproducible, prolonged transit time, through the gastrointestinal tract, of the subunits of a multiple-units dose.

According to the invention, therefore, a controlled-release multiple-units drug dose comprises a tablet or capsule enclosing encapsulated pellets, granules or crystals of a therapeutically active agent, the specific weight of at least some of which has been increased to a specific weight of at least 1.4 by means of a physiologically inert or innocuous substance of higher specific weight than that of the therapeutically active agent.

The said increase of the specific weight ensures that the units get a specific weight exceeding that of the normal gut contents.

The increase can be attained e.g. by incorporating the physiologically inert or innocuous substance in the core or the coating material of the pellets or the coating material of the microencapsulated crystals, or in any other known way.

Examples of substances, which can be used to increase the specific weight of the subunits in a controlled-release multiple-units dose, are barium sulphate, zinc oxide, titanium dioxide, and iron powder produced by reduction (ferrum reductum).

The use of a controlled-release multiple-units dose is also advantageous because dispersal of the subunits along the gastrointestinal tract results in lower local concentration of the active substance, thus causing less irritation of the mucosa in case of irritative drugs.

Since a greater specific weight tends to increase the transit time of the subunits, obviously a combination of lighter and heavier subunits in a multiple-units dose has the effect of further dispersing the units along the gastrointestinal tract. Mixing of subunits of different specific weight and/or with different active agents could also be advantageous in the formulation of a controlled-release multiple-units combined product.

The controlled, prolonged drug release means also that unnecessary peak concentrations in the blood with their inherent risks of exaggerated drug action or enhanced side effects of both are avoided and that adequate treatment over extended time periods is ensured.

Clinical investigations have shown that the transit time of the individual units of a multiple-units dose can easily be extended over a 24 hours period by suitably increasing the specific weight of the subunits.

Thus, according to the invention, a substantial proportion, e.g. at least 5% and preferably at least 20%, and sometimes at least 50%, by weight of the total composition is in the form of subunits having specific weight greater than the specific weight of the entire drug composition. The amount by which the specific weight of some of the subunits is above the average can vary widely, but preferably it is at least 5% above the average and preferably at least 20%. Expressed in another way at least 25% by weight of the subunits preferably have a specific weight at least 25% above the specific weight of other subunits in the composition.

Although the drug release from the subunits of the multiple-units dose can be controlled in various known ways, the preferred manner of controlling is by coating the subunits with a diffusion membrane which is insoluble in and not degradable by the gastrointestinal juices.

The subunits can be composed as follows. An inactive, heavy core can be provided with a layer of the active agent by means of a suitable adhesive, and then provided with a diffusion membrane.

Alternatively, the active agent can be mixed with the innocuous heavy substance, the mixture being formed to pellets or granules, and coated with the diffusion membrane.

A third possibility is using crystals of the active agents as cores in the subunits.

In all cases, the amount and specific weight of the inactive substance determines the increase in specific weight of the subunits.

A pilot study was aimed at observing the influence on transit time of variations in specific weight and size of the subunits. Four ileo-colostomy patients, three females and one male, aged between 24 to 40 years, three with part of the small intestine resected, volunteered for the study. The post-operative period was from 2 to 6 months. As determined the day before the investigation, each patient had a gastrointestinal transit time of at least 2½ hours.

Coated pellets were used, prepared either with barium sulphate (specific weight of pellets 1.6 g/ml) or with paraffin wax (specific weight of pellets 1.0 g/ml). In both cases, the diameters were 0.3–0.7 mm and 1.2–1.7 mm, respectively.

After a 12 hours fasting period, a transparent colostomy bag was fitted to the patient, and 1850 pellets suspended in a standard meal were administered. After this meal, the patients resumed the usual hospital meal routine.

The investigation period was 36 hours. During the first 12 hours, the colostomy bag was totally emptied every 3 hours, during the next 12 hours intermittently as needed, and during the final 12 hours again every 3 hours.

The contents from each emptying were investigated separately, counting the contents of the four different types of pellets to determine the transit time.

The following tables illustrate the results of the investigations.

Table 1

Number, size, and specific weight of the pellets			
Number of pellets	Diameter		Total
	0.3–0.7 mm	1.2–1.7 mm	
Light pellets sp.w. 1.0 g/ml	800	125	925
Heavy pellets sp.w. 1.6 g/ml	800	125	925
	1600	250	1850

Table 2

Recovery of pellets			
Patient	Sp. weight	Diameter	
		0.3–0.7 mm	1.2–1.7 mm
EBO	1.0	87.9%	98.4%
	1.6	95.6%	96.0%
IMC	1.0	88.9%	95.2%
	1.6	64.9%	64.8%
MH	1.0	76.1%	67.2%
	1.6	71.3%	41.6%
PKB	1.0	89.8%	95.2%
	1.6	72.5%	77.6%

Table 3

Average transit time for pellets in hours									
Sp.w.	Diam.	EDO		IMC		MH		PKB ¹⁾	
		0.3–0.7	1.2–1.7	0.3–0.7	1.2–1.7	0.3–0.7	1.2–1.7	0.3–0.7	1.2–1.7
1.0		3.2	1.8	6.5	7.9	12.9	16.9	9.0	9.8
1.6		13.5	9.5	23.7	27.3	16.0	19.3	10.7	10.1

¹⁾One colostomy bag was lost during the 5th interval of the investigation period. The number of each type of pellets in the lost bag has been calculated on the assumption that the probability of recovery would be equal to that of EBO.

The extension of the transit time attained by an increase of the specific weight of the pellets is clearly demonstrated by Table 3.

Continued clinical investigations comprised six ileo-colostomy out-patients, five females and one male, aged between 25 and 50 years. Two of the patients had part of the ileum resected.

Participation in the study was conditional upon the patient having terminated a post-operative period of 2 months and having a transit time at least 3 hours, as determined on the day before the examination.

Coated pellets identical to those in the pilot study were used.

In the morning of the day of examination, the fasting (12 hours) ileo-colostomy patient had a transparent colostomy bag fitted, and at the same time 250 pellets of each of the four kinds, or a total of 1000 pellets, were administered, suspended in a standard meal.

After the test meal, the patient resumed the usual meal and locomotive routine. The colostomy bag was emptied completely every 2 hours during the first 14 hours, and then every 4 hours during the following 8 hours of night. The pattern of emptying was repeated the following day in order to complete a 48 hours' observation period.

The collected fractions were analysed by manually picking off the pellets from thin layers of the visceral contents.

The frequency of pellets in the colostomy bags during the first day, defined as the period from 8 a.m. to 2 a.m., is shown in Table 4. The difference in frequencies of the four types of pellets having passed the small intestine during the first day is seen to be caused mainly by the differences in specific weight of the pellets, the influence of the different diameters of pellets being less important.

Table 4

Frequency (%) ⁽¹⁾ of pellets during the first day of observation								
Size mm	Specific weight	Patients						Average
		BMM	VN	AS ⁽²⁾	HR	JPL	IO ⁽³⁾	range
0.3–0.7	1.0	100.0	100.0	91.9	90.4	100.0	97.7	97.6
	1.6	17.2	6.3	77.0	9.8	16.4	16.6	13.3
1.2–1.7	1.0	99.1	99.6	99.2	77.2	96.8	87.6	92.1
	1.6	10.9	4.4	68.8	2.1	3.4	5.4	5.2

⁽¹⁾Relative to recovered pellets. The average of recovered pellets of all four kinds in the total observation period was 90% (range 84–95%).

⁽²⁾The patient AS is atypical, owing to a very large consumption of liquid, totalling 5900 ml (thereof 5000 ml of beer), during the test period.

⁽³⁾The figures for the patient IO is the average of two replicate studies.

The figures shown that the specific weight is of significant importance ($p < 0.05$) for the prolongation of the transit time of the subunits, whereas it is doubtful whether an increase in size is of importance.

The following Examples illustrate different ways of preparing pellets with increased specific weights for use in controlled-release multiple-units doses.

EXAMPLE 1

The components of the core of a pellet are:

	Parts by weight
Ferrum reductum	80
4-(2-Hydroxy-3-isopropylaminopropoxy)-indole	6
Microcrystalline cellulose	6
Talcum	2
Hydroxypropylcellulose	3
Sodium hydrogen carbonate	3

The components are mixed and moistened with 20 parts by weight of water, after which the mass is extruded to form strings of 1 mm diameter, from which balls of approximately 1 mm diameter are formed. After drying, the specific weight of the balls is 3.7.

The balls are coated with a solution of an acrylic polymer, marketed under the registered trade mark Eudragit RS, the specific weight being 3.4 after the coating.

EXAMPLE 2

The core components of a pellet are:

	Parts by weight
Zinc oxide	95
Polyethylene powder	5

The components are mixed, moistened with 16 parts by weight of water, and extruded to strings of 0.8 mm diameter, from which balls with about the same diameter are formed. After drying, the specific weight of the balls is 3.0.

The cores are then coated with 15 parts by weight of ethylphenylephrine hydrochloride (α -[(ethylamino)methyl]m-hydroxybenzyl alcohol hydrochloride) by alternatively moistening with a 3% solution of ethylcellulose in isopropanol and coating with the powdered drug.

Finally, an external coating is applied, consisting of ethylcellulose with 10% by weight of acetyltributyl citrate admixed as a softening agent.

The specific weight of the resulting pellets is 2.7.

EXAMPLE 3

The components of the subunits are:

	Parts by weight
Acetylsalicylic acid crystals	65
Titanium dioxide	32.5
Acrylic polymer (Eudragit ® RS)	2.5

In a coating pan, the crystals of acetylsalicylic acid (specific weight 1.37) are alternatively moistened with a 3% solution of the acrylic polymer, and dusted with titanium dioxide powder.

The specific weight of the resulting coated crystals is 1.6.

We claim:

1. A controlled release upper-gut retentive gastrointestinal tract transit time increasing multiple-units drug dose, which comprises a tablet or a capsule, enclosing subunits of a therapeutically active agent in the form of 0.3 to 1.7 millimeter balls or pellets, each of which are enclosed in an insoluble dialysis membrane of a cellulose ether or acrylic polymer allowing for diffusion of the juices of the gastrointestinal tract, the specific weight of at least 25% by weight of which subunits has been increased from 1.0 or less to at least 1.4 by means of a physiologically innocuous substance of higher specific weight than that of the therapeutically active agent.

2. A controlled release upper-gut retentive gastrointestinal tract transit time increasing multiple-units drug dose, which comprises a tablet or a capsule, enclosing subunits of a therapeutically active agent in the form of spherical 0.3 to 1.7 millimeter balls or pellets, each of which are enclosed in an insoluble dialysis membrane of ethyl cellulose or acrylic polymer allowing for diffusion of the juices of the gastrointestinal tract, the specific weight of at least 25% by weight of which subunits has been increased to at least 1.4 by means of barium sulfate, zinc oxide, titanium dioxide or ferrum reductum, as a physiologically innocuous substance of higher specific weight than that of the therapeutically active agent, and the other subunits in the drug dose have an otherwise unchanged specific weight of 1.0 or less.

3. A drug dose as set forth in claim 2, in which the specific weight of at least some of the subunits is at least 1.6.

4. A drug dose as set forth in claim 2, in which subunits of different specific weights contain different therapeutic agents.

* * * * *

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WILLIAM M. HOBBY, III, ESQ.
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ASSIGNOR:
LIN, J.T.

DOC DATE: 03/25/94

RECORDATION DATE: 03/25/94 NUMBER OF PAGES 002 REEL/FRAME 6939/0975

DIGEST : ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
LASERSIGHT, INC.
3251 PROGRESS DRIVE
SUITE B
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SERIAL NUMBER 8-218319
PATENT NUMBER

FILING DATE 03/25/94
ISSUE DATE 00/00/00

EXAMINER/PARALEGAL
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To the Applicable Commissioner of Patents and Trademarks: Please record the attached documents or copy thereof.

1. Name of conveying party(ies):
J.T. LIN

2. Name and address of receiving party(ies):
Name: Lasersight, Inc.

Internal Address:

Street Address: 3251 Progress Drive
Suite B

City: Orlando
Zip: 32826

State: FL

Additional name(s) of conveying party(ies) attached? Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Security
☐ Merger ☐ Agreement
☐ Change of Name
☐ Other

Execution Date: March 25, 1994

Additional name(s) & address(es) attached? Yes ☐ No ☒

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: March 25, 1994

A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? Yes ☐ No ☒

5. Name and address of party to whom correspondence concerning document be mailed:

William M. Hobby, III, Esq.

6. Total number of applications and patents involved: One (1)

7. Total fee (37 CFR 3.41)....\$ 40.00

☒ Enclosed

Internal Address:

Hobby & Beusse
157 E. New England Avenue
Suite 375
Winter Park, FL 32789

Authorized to be charged to deposit account

8. Deposit account number:

Street Address: Same as above

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William M. Hobby, III
Name of Person Signing

Signature

03/25/94

Date

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A S S I G N M E N T

08/218319

WHEREAS, Dr. J.T. Lin
 hereinafter referred to as assignor, has made certain improvements
 or inventions in OPHTHALMIC SURGERY METHOD USING NON-CONTACT
SCANNING LASER for which said assignor has executed
 an application for United States Letters Patent on the 25th day of
March 1994; and

WHEREAS, LaserSight, Inc.
 hereinafter referred to as assignee, is desirous of acquiring the
 same;

NOW THEREFORE, This Indenture Witnesseth: That for and in
 consideration of ONE DOLLAR, lawful money of the United States and
 other good and valuable consideration, receipt whereof is hereby
 acknowledged, said assignor does hereby sell, assign, and transfer
 to said assignee, its successors and assigns, all right, title and
 interest in and to said U.S. Patent Application, the invention or
 inventions therein shown and described and any improvements on said
 inventions heretofore or hereafter made, any divisions of
 continuations of said application, and all patents, United States
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 invention or inventions thereof, and any reissues, continuations or
 extensions of said patents; and said assignor does hereby authorize
 and request the Commissioner of Patents to issue all patents on
 said United States Patent applications or for the invention or
 inventions hereof, in accordance with this assignment.

And said assignor for said consideration hereby covenants and
 agrees that said assignor is the owner of the full title herein
 conveyed and has the right to convey the same, and agrees that said
 assignor will communicate to said assignee, any facts known to said
 assignor respecting said invention or inventions, and testify in
 any legal proceedings when called upon by said assignee, sign all
 lawful papers deemed by said assignee as expedient to vest in it
 the legal title herein sought to be conveyed or for the filing and
 prosecution of all applications and patents, United States and
 foreign, and otherwise aid said assignee, its successors and
 assigns, in obtaining full patent protection on said invention and
 enforcing proper protection under said patents, but in every
 instance at the assignee's expense.

Signed and sealed this 25th
 day of MARCH, 1994.

Dr. J.T. Lin RECORDED
 PATENT & TRADEMARK OFFICE

STATE OF FLORIDA:
 COUNTY OF ORANGE :

MAR 25 94

The foregoing instrument was acknowledged before me this 25th
 of MARCH, 1994 by Dr. J.T. Lin, who ☒ is personally known
 to me or who has produced as
 identification and who did/did not take an oath.

William M. Hobby
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REEL 6939 FRAME 976